REMARKS

New claims 18-24 are directed to methods of reducing the adherence of *staphylococcus saprophyticus* to epithelial cells. In that the art of record offers no teaching with regard to taurolidine's use against this microoganism's adherence to epithelial cells, these claims clearly distinguish beyond the art of record.

New claims 25-35 are rewritten versions of cancelled claims 7-17. In their rewritten forms these claims each contain the further element that the taurolidine concentration is from about 0.05% w/v to about 2.0% w/v and is maintained for about a thirty minute contact time. These new rewritten claims clearly distinguish beyond the art of record. However, in light of the Examiner's previous arguments against the now cancelled claims, Applicant offers the following additional comments supported by the herewith-attached rebuttal art.

The New Claims in view of the Examiner's Previous Claim Rejections under 35 U.S.C. §112

Cancelled dependent claims 13-16 and cancelled independent claim 17 were rejected under 35 U.S.C. §112, ¶1. The Examiner asserted that these claims presented elements for which the specification did not contain adequate descriptive support. And further, that without such descriptive support the specification would not convey to the artisan that, at the time of filing, the Applicant was in possession of the claimed subject matter. It was ultimately asserted that the introduction of these claim elements

constituted new matter. *Each* of new claims 31-35 are directed to methods of using taurolidine *to reduce the adherence of microorganisms to epithelial cells.*

In the *prior* Office Action the Examiner had similarly rejected claims *7-12* under §112, ¶1, asserting that the specification did not support the claimed methods for reducing the adherence of microorganisms to epithelial cells. At that time, the Examiner further asserted that the term "epithelial cells" was not even mentioned in the specification. In response to *those* particular assertions, Applicant offered a four paragraph excerpt from the specification (pages 9 & 10) wherein Taurolidine's ability to reduce the adherence of microoganisms to epithelial cells was discussed *ad nauseum* and with specificity. That the Examiner chose not to maintain *that earlier* §112, ¶1 rejection with regard to claims 7-12, was his tacit concession that the specification does indeed disclose Taurolidine's ability to reduce the adherence of microoganisms to epithelial cells, and that it does so in a manner that would convey to the artisan the Applicant's possession of *that* general subject matter.

In order to reject claims 31-35, under the first paragraph of 35 U.S.C §112 for lack of descriptive support, it is incumbent upon the examiner to establish that the originally-filed disclosure would not have reasonably conveyed to one having ordinary skill in the art that Applicant had possession of *this* claimed subject matter. Wang Laboratories, Inc. v. Toshiba Corp., 993 F.2d 858 (Fed Cir. 1993). Adequate description under the first paragraph of 35 U.S.C. §112 does not require **literal** support for the claimed invention. In re Herschler, 591 F.2d 693 (CCPA 1979). In re Edwards, 568 F.2d 1349 (CCPA 1978). In re Wertheim, 541 F.2d 257 (CCPA 1978). Rather, it is sufficient

if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that Applicant had possession of the **concept** of what is claimed. In re Anderson, 471 F.2d 1237 (CCPA 1973).

Clearly, the Examiner's failure to maintain the *earlier* §112 rejection demonstrates Applicant's possession of the **concept** of using taurolidine to reduce the adherence of microoganisms (in general) to epithelial cells (in general). Claims 31-35 claim that same general method except where the microorganism is a **urine isolate** of *escherichia coli* adhering to **human buccal** epithelial cells and where the microorganism is an **oral isolate** of *candida albicans* adhering to **human uro**epithelial cells.

While only the general **concept** need be disclosed to satisfy §112 ¶1, Applicant's specification does indeed contain **literal** descriptive support for these claim elements:

> "**Taurolidine has been found to significantly reduce the adherence** of buccal and vaginal isolates **of candida albicans** blastospores **and** urine isolates of **escherichia coli** and staphylococcus saprophyticus to **epithelial cells. Light microscopy and radioisotopic counting methods were used to quantify the adherence of the microorganisms to either uroepithelial or buccal epithelial cells.**
>
> **Treatment of either epithelial cells or microorganisms with taurolidine resulted in reduced adherence of microorganisms.**" (Specification, page 9, emphasis added).

Clearly, the instant specification discloses the use taurolidine to reduce the adherence of microorganisms to epithelial cells, and its use wherein those microorganisms are *C. albicans* or *E. coli*, and its further use wherein the epithelial cells are uroepithelial cells or buccal epithelial cells. That claims 31-35 contain negative limitations disclaiming certain of these disclosed aspects would not render theses claims violative of §112, ¶1. Particularly instructive on this point is the opinion of the Federal Circuit's predecessor court in Application of Johnson,:

> "The notion that one who fully discloses, and teaches those skilled in the art how to make and use, a genus and numerous species therewithin, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and has thus failed to satisfy the requirements of s 112, first paragraph, appears to result from a hypertechnical application of legalistic prose relating to that provision of the statute. All that happened here is that appellants narrowed their claims to avoid having them read on a lost interference count."
>
> "Here, as **we hold on the facts of this case**, the "written description" in the 1963 specification supported the claims in the absence of the limitation, and **that specification having described the whole, necessarily described the part remaining**. The facts of the prosecution are properly presented and relied on, under these circumstances, to indicate that appellants are merely excising the invention of another, to which they are not entitled, and are not creating an "artificial subgenus" or claiming "new matter." 558 F.2d 1008 at 1019 (C.C.C.P. 1977)(emphasis added).

Like the appellants in Johnson, Applicant having disclosed the whole of his concept is free to disclaim a qualified portion of it without raising issues of new matter.

The New Claims in view of the Examiner's Previous Claim Rejections under 35 U.S.C. §102

Cancelled claims 7 and 9 were rejected under 35 U.S.C. §102(b) as being anticipated by Blenkharn (Surgical Res. Comm.; Vol. 2, pp 149-155; 1987; hereinafter "Blenkharn"), for reasons made of record in the Office Action mailed December 12, 2001. Claims 7-9, 11 and 12 were also rejected under 35 U.S.C. §102(b) as being anticipated by Gorman (Journal of Pharmacy and Therapeutics; Vol. 12; pp. 293-399; 1987; hereinafter "Gorman"), for reasons made of record in the Office Action mailed December 12, 2001.

However, none of their rewritten counterparts currently presented as new claims 25-27, 29 and 30 would be anticipated by either of the Blenkharn or Gorman references.

Anticipation under 35 U.S.C. §102 requires that each and every element of the claimed invention be *identically* disclosed in a *single* prior art reference. Diversitech Corp. v. Century Steps, Inc., 850 F.2d 675, 677 (Fed. Cir. 1988). Additionally, the *single* prior art reference must disclose those elements *as they are arranged in the claim in question.* Lindemann Maschinenfabrik Gmbh v. American Hoist and Derrick Company, 730 F.2d 1452, 1458 (Fed. Cir. 1984). Finally, the single prior art reference is *not* anticipating if it does not disclose an identity of *structure*, *purpose*, and *result* with the claimed invention. Tate Engineering, Inc. v. United States, 477 F.2d 1336, 1342 (Court of Claims 1973).

A. Claims 25 & 27 in view of Blenkharn

Claim 25 is directed to a method of *reducing* the adherence of microorganisms to epithelial *cells* by treating either with taurolidine. The nearest instruction in Blenkharn's disclosure is that taurolidine "has marked anti-adhesive properties with regard to the **prevention** of peritoneal adhesions and the adhesion of micro-organisms to epithelial **surfaces**." (Blenkharn, Abstract, emphasis added). The Examiner argued against the cancelled claims that "one of ordinary skill in the art" would consider Applicant's distinction between epithelial *cells* and epithelial *surfaces* a nullity. Applicant responded then, and repeats now, that insofar as the Examiner then made an *anticipation* rejection it would not matter what "one of ordinary skill in the art" would consider epithelial to mean. The proper analysis for an *anticipation* rejection is that delimited above. Furthermore, claim 25 is directed to the *reduction* of adherence, not to the *prevention* of adherence.

Claim 27 adds to claim 25 the further element that the microorganisms are *urine isolates* of *escherichia coli.* The Examiner had offered from Blenkharn's disclosure that "[d]etectable endotoxin concentrations subsequent to exposure of *Escherichia coli* to antibiotics were reduced up to 20-fold by taurolidine." (Blenkharn, Abstract). Applicant does not dispute that Blenkharn teaches that taurolidine can diminish the effects of, or neutralize, endotoxin. Indeed, Applicant's own disclosure instructs that taurolidine possesses such qualities:

> "**This compound also has the ability to neutralize endotoxin** in vitro and it also exhibits marked anti-adherence properties in vitro. (Specification page 3, lines 13-14, emphasis added).
>
> "**The compound demonstrates endotoxin neutralizing activity**, inhibits adherence, is more active at low pH which may prevail at the site of infections or within phagolysosomes, is slightly more active when tested in serum-supplemented media, and inhibits potential bacterial toxins such as staphylococcal coagulase." (Specification page 4, lines 16-20, emphasis added).

But, claim 27, like claim 25, is directed toward *reducing adherence*, not toward reducing "*endotoxin concentration.*" Furthermore, it is an element of claim 27 that the microorganism be a *urine* isolate of *Escherichia coli.* Applicant had previously argued that Blenkharn is silent as to this "urine" aspect, and the Examiner responded that "*Escherichia coli* is the same no matter how the microorganism is isolated." To rebut that position Applicant submits two references: *Characterization of Clinical and Environmental E. coli Isolates from an Integrated Turkey Operation*, by Altekruse *et al.* (hereinafter "Altekruse") **Exhibit A**; and *Genomic Typing of Escherichia coli Isolates from Human, Animal and Environmental Sources by Random (RAPD) Analysis*, by Ting *et al.* (hereinafter "Ting") **Exhibit B**. Altekruse discloses that the *fecal* and *clinical* isolates of *E. coli* studied on a turkey farm had dissimilar biochemical phenotypes. Ting

is a progress report of an environmental grant focused on developing methods to identify the host source of water pollutant *E coli* bacteria. Ting examined 65 human *E. coli* isolates (3 fecal, 30 urine, and 32 blood) and 3 cow *E. coli* isolates (all fecal). Ting discloses that:

> "All three human fecal isolates were correctly identified as human *E. coli* and all three cow *E. coli* samples were also correctly identified as cow *E. coli*. Among the 30 human urine and 32 human blood isolates, 28 and 29, respectively, were determined to be human *E. coli*." (page 3, ¶5)

Altekruse and Ting betray the Examiner's position with regard to the negligibility of the "urine isolate" claim element, and they demonstrate that *E. coli* isolates can differ both within a host source and between host sources. Accordingly, Blenkharn does not disclose the *identical structural elements as they are arranged* by claims 25 & 27.

Moreover, neither Blenkharn's *purpose*, nor its *result*, is concerned with *reducing adherence*, as instantly claimed. Blenkharn is concerned with gauging taurolidine's propensity to interact with antibiotics (Table I); its potential for *Endotoxin Neutralization* (point heading p. 151); its comparative antibacterial efficacy vis-a-vis conventional antibiotics (Table II); and its synergies, or lack thereof, when administered in combination with those conventional antibiotics (*Antibiotic Combinations with Taurolidine* p. 153). These *purpose* and *result* are further manifested in the following excerpt from Blenkharn's concluding paragraph:

> "**The <u>results</u> of this study highlight the endotoxin-neutralizing activity of taurolidine**, up to 20-fold reduction in endotoxin concentration, **and lack of antagonism when combined with commonly used antibiotics** active against Gram negative bacteria. **On the basis of this data, it appears that taurolidine may be safely co-administered with any of these agents**, although not with vancomycin, without prejudice to the antibacterial activity. **Controlled trials of taurolidine in combination with bactericidal antibiotics are now warranted to**

> **determine more precisely its role as a specific anti-endotoxin compound in severe Gram negative sepsis.**" (Blenkharn page 155).

By contrast, the *purpose* and *result* of the instant invention is to *reduce the adherence of microorganisms to epithelial cells*, which purpose and result the specification instructs upon thoroughly:

> "Taurolidine has been found to significantly reduce the adherence of buccal and vaginal isolates of candida albicans blastospores and urine isolates of escherichia coli and staphylococcus saprophyticus to epithelial cells. **Light microscopy and radio-isotopic counting methods were used to quantify the adherence of the microorganisms to either uropithelial or buccal epithelial cells.**
>
> Treatment of either epithelial cells or microorganisms with taurolidine resulted in reduced adherence of microorganisms.
>
> **Using a thirty minute contact time, a range of taurolidine concentrations on the order of 0.05% to about 2.0% w/v were examined for antiadherence activity. Significant decreases in candida blastospore adherence were observed at concentrations of less than 0.1% w/v taurolidine. Maximum reductions in adherence, on the order of about 65% of control were observed when concentrations of taurolidine greater than about 0.5% w/v. Increasing the taurolidine concentration beyond this level did not produce a concomitant increase in antiadherence activity. Conversely, dilution of taurolidine concentration may proceed to a considerable extent before its capacity for antiadherence is lost.**
>
> **The foregoing demonstrates that taurolidine exerts an antiadherence activity via a chemical modification of the outer surface structures such as fimbriae causing agglutination or disappearance of the structures.** The effect of taurolidine on these structures which contribute to the initiation of infection and in determining the pathogenicity of the organism is clear evidence of one aspect of taurolidine's mechanism of action in preventing infection or reducing its severity." (Specification pages 9 & 10, emphasis added).

Clearly, Blenkharn does not disclose the use of taurolidine to *reduce* the adherence of microorganisms to epithelial *cells*. Accordingly, not only does Blenkharn fail to identically disclose *each* and *every structural element as they are arranged* by claims 25 & 27, it further fails to disclose their identical *purpose* and *result*. Therefore, Blenkharn would fail to anticipate new claims 25 & 27.

B. Claims 25-27, 29 & 30 in view of Gorman

Gorman discloses only that taurolidine exhibits anti-adherence activity in two *specific* adherence systems. The first is one wherein the microorganism is an *oral isolate of Candida albicans* and the epithelial cells are *human buccal epithelial cells*. The second is one wherein the microorganism is a *urine isolate of Escherichia coli* and the epithelial cells are *human uroepithelial cells*. These very specifically limited disclosures do not anticipate claims 25-27, 29, & 30. Each of these new claims are directed to *methods for reducing adherence of microorganisms to epithelial cells*, they are not directed to *adherence systems*, as disclosed by Gorman; much less are they directed to Gorman's two *specific* adherence systems.

The instant claims do not present any genus of which Gorman's adherence systems would constitute an anticipating species.[1] Claim 25's scope conceives of *microorganisms* (generally) adhering to *epithelial cells* (generally). Claim 26 conceives of *two specific types of isolates* of a *specific microorganism strain* adhering to *epithelial cells* (generally). Claim 27 conceives of a *specific type of isolate* of a *specific microorganism strain* adhering to *epithelial cells* (generally). Claims 29 and 30 conceive of *microorganisms* (generally) adhering to a *specific type of epithelial cell*. By contrast, the adherence systems of Gorman each disclose a *specific type of isolate* of a *specific microorganism strain* adhering to a *specific type* of *epithelial cell* derived from a *specific host*.

As the above-cited Altekruse and Ting references disclose *E. coli* isolates can differ both *within* a host source and *between* host sources. One would expect similar

[1] If a genus/species relationship had been arguable the Examiner would surely have included cancelled claim 10 in his earlier §102 rejections of cancelled claims 7-9, 11, and 12.

variance among other strains of microorganisms, such as *Candida albicans*. For example, Gorman's narrow disclosure of taurolidine having antiadherence properties in an **orally isolated** *Candida albicans* (human strain isolated "from denture stomatitis")/ **human buccal** epithelial cell system, would not anticipate the method of claim 26, wherein the adherences of both **buccally isolated** and **vaginally isolated** *C. albicans* (host indifferent) are necessarily *co-reduced* against epithelial cells which are not necessarily **human** or **buccal**. Gorman's two *host–specific* antiadherence systems do not constitute an anticipating species.

The non-anticipating nature of Gorman is further underscored by the fact that in his adherence systems:

> "Each of the three agents exhibited significant anti-adherence activity which was **concentration dependent**." (Gorman, Summary, page 393, emphasis added).

That relationship was not observed for taurolidine in the instant specification:

> "Maximum reductions in adherence, on the order of about 65% of control were observed when concentrations of taurolidine greater than about 0.5% w/v. **Increasing the taurolidine concentration beyond this level did not produce a concomitant increase in antiadherence activity. Conversely, dilution of taurolidine concentration may proceed to a considerable extent before its capacity for antiadherence is lost.**" (Specification, page 10, emphasis added).

The New Claims in view of the Examiner's Previous Claim Rejections under 35 U.S.C. §103

In the Final Office Action the Examiner maintained his §103 rejection of cancelled claim 10 over Gorman in view of Blenkharn. New claim 28, a rewritten version of cancelled claims 10, depends from new independent claim 25 adding the

further claim element that the microorganism is specifically *Staphylococcus saprophyticus*. As argued earlier, Gorman discloses two adherence systems, one consisting of *Candida albicans* the other of *E. coli*. Gorman does not mention or suggest *Staphylococcus* microorganisms of any kind. And Blenkharn only instructs that:

> "**With *S. aureus***, combinations of **taurolidine and aminoglycoside** (gentamicin or amikacin) **were synergistic** (FIC index 0.3 and 0.4 respectively) although **combinations with vancomycin were antagonistic** (FIC index 2.3)." (Blenkharn page 153, emphasis added).

In other words, vis-a-vis *Staphylococcus aureus* taurolidine helps one drug and hinders another. In light of this limited *Staphylococcal* teaching Applicant previously argued that no generalism with regard to *Staphylococcus* and taurolidine could be gleaned from Blenkharn alone. The Examiner now rebutted that conclusion by bolstering Blenkharn with an *additional* reference—U.S. Patent 5,595,742 issued to Fujwara. But, contrary to the Examiner's position, Blenkharn's assertion that "[t]aurolidine has a uniquely broad spectrum of antibacterial and antifungal activity" (Abstract), is not "further evidenced by the Fujiwara patent." Fujiwara discloses the use of an extract of *Ganoderma lucidum* for treating *Staphylococcal* infection; it does not mention taurolidine in any way. It is therefore wholly irrelevant to examination of the cancelled or instantly presented new claims. It would appear to have been the Examiner's position that since Fujiwara teaches *Ganoderma lucidum* extract to treat *Staphylococcus* genus—such as *saprophyticus*—and since *Ganoderma lucidum* extract is an antimicrobial agent—like taurolidine—therefore taurolidine is necessarily an obvious agent to treat *Staphylococcus saprophyticus*. Such an attenuated extrapolation would necessarily mean that all antimicrobials were obvious for treating *Staphylococcus saprophyticus*.

The Examiner also seemed to argue that the use of taurolidine *to reduce the adherence* of *Staphylococcus saprophyticus* would be obvious in light of Blenkharn's disclosure of both taurolidine's "uniquely broad spectrum of antibacterial and antifungal activity" and its use to *treat Staphylococcus aureus*. But, as indicated by the hereto-attached reference *Activities of Taurolidine In Vitro and in Experimental Enterococcal Endocarditis*, by C. Torres-Viera *et al.*, Antimicrobial Agents and Chemotherapy, June 2000, p. 1720-1724, Vol. 44, No. 6 (hereinafter "Torres") **Exhibit C**, it is not possible to generalize as to the *in vivo* effectiveness of taurolidine in treating infection caused by microorganisms. The Torres reference—authored by doctors at Beth Israel Medical Center and Harvard Medical School regarding research conducted *circa* the instant application's filing date—clearly demonstrates that taurolidine does not necessarily have broad-spectrum activity. In two separate rat models (Sprague-Dawley and Wistar) Torres found that taurolidine was ineffective against infections due to *E. faecium*. Torres found that taurolidine was equally useless in rat models against vancomycin-resistant *enterococci* and methicillin-resistant *Staphyloccocus aureus*:

> "To determine whether taurolidine activity could be demonstrated in vivo in our experimental model, we employed the maximum doses which could be physically administered with combined i.v. plus i.p dosing. Even with such doses, **we were unable to show activity *in vivo* against either test organism in this model.**" (Torres page 4 of 6, emphasis added).

And, Torres concludes that taurolidine might *not* be able to achieve the necessary minimum inhibitory concentrations to be effective against some strains:

> **"Because peak concentrations of taurolidine and its metabolites determined to date in the plasma of humans do not appear to reach the MICs [Minimum Inhibitory Concentrations] against many of the strains of concern, it seems doubtful that this drug would have a significant role in the systemic therapy of established infections."** (Torres, page 4 of 6, emphasis added).

Torres' disclosure of the failings of taurolidine against several different organisms seriously undermines the extent to which the Examiner can rely on Blenkharn's "broad-spectrum" generalism in examining the new claims. Therefore, *at the time the invention was made* the artisan having studied Blenkharn would have viewed Blenkharn's taurolidine disclosures regarding *Staphylococcus aureus* speciously. That skepticism would most certainly have deterred the artisan from ascribing to taurolidine the panacean effectiveness against *Staphylococcal* genus that the Examiner earlier asserted to meet the *saprophyticus* species claim element of cancelled claim 10. The artisan would appreciate taurolidine's antiadherence aspects as against the *saprophyticus* species only after resort to the instant specification as a hindsight guide.

Moreover, the *proper* question under 35 U.S.C. § 103 is not whether the *differences* between the claims and the prior art would have been obvious, but rather, whether the claimed invention *as a whole* would have been obvious. Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530 (Fed. Cir. 1983). This determination requires that a prior art reference *also* be considered *as a whole*—in its entirety. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540 (Fed. Cir. 1983). By selectively relying on the two isolated excerpts from Blenkharn the rejection fails to consider the teaching of the reference as a whole. As stated above, Blenkharn discloses that taurolidine has a "uniquely broad spectrum of antibacterial and antifungal activity" and is used to treat *Staphylococcus aureus*. Yet, when viewed *as a whole*, neither of these disclosures would commend taurolidine's utility to *reduce the adherence* of *Staphylococcus saprophyticus to epithelial cells*, and thereby, lead the artisan to the instant claims. Succinctly, nothing

in the art suggests the use of taurolidine to reduce the adherence of *S. saprophyticus* to epithelial cells.

In view of the foregoing, Applicant submits that claims 18-35 are patentable in view of the art previously made of record by the Examiner, as that art is both discussed above and rebutted by the art attached hereto. It appearing that the application is in condition for allowance, Applicant requests its prompt passage to issue.

It is believed that no fee is due. However, if any fee is due it should be charged to Deposit Account No.: 03-0678.

CERTIFICATE OF MAILING

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